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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/008,385	11/12/2001	Carol W. Readhead	20040351.DIB	3519

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EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/008,385	READHEAD ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *135,137,138,140-143 and 145-160* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *135,137,138,140-143 and 145-160* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.00

DETAILED ACTION

Mr. Mersereau called on July 11, 2005 and indicated that claim 160 had not been included in the Final Rejection, filed April 6, 2005. The Examiner indicated that claim 160 had inadvertently been left out and no analysis of claim 160 had been carried out. As such, the Examiner agreed that a new action would be sent out. Thus, the Final Rejection filed April 6, 2005 is vacated.

Applicant's response to the First Action on the Merits was filed August 30, 2004. Claims 135, 140, 145-146, 153 have been amended. Claims 156-159 are added. Claims 136, 139, 144 are canceled.

An amendment to the claims filed October 5, 2004, adds new claim 160.

An amendment to the claims filed October 14, 2004 amends claims 156-157.

Claims 135, 137, 138, 140-143, 145-160, drawn to an *in vitro* method of incorporating a polynucleotide encoding a desired trait into a male germ cell and to a transgenic animal produced by the method, are under consideration.

Information Disclosure Statement

The information disclosure statement filed May 20, 2004 and August 30, 2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which

caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

With regards to the foreign patent documents (see IDS, May 20, 2004), the even numbered pages are missing. These must be provided in order to be considered. Citation 54, 76, 78 are not in proper citation format. Author, journal, year of publication, volume of publication, and pages must be provided.

The Nguyen et al. reference cited on the IDS filed August 30, 2004 is missing. This must be provided in order to be considered.

Withdrawn Rejections

35 U.S.C § 112, first paragraph-Written Description

The rejection under 35 U.S.C. § 112, first paragraph, written description, with regards to claims 140 and 141, has been withdrawn. Applicant has amended claim 140.

35 U.S.C. § 112, second paragraph

The rejection under 35 U.S.C. § 112, second paragraph, with regards to claims 139 and 146, has been withdrawn. Applicant has cancelled claim 139 and amended claim 146.

35 U.S.C.§ 102(a), 102(b) and 102(e)

Applicant's arguments regarding 35 U.S.C §102(b), anticipated by Bachiller et al., 1991, see page 9 of Applicant's Response, August 30, 2004, with respect to claims 135, 136, 138, 139, 144, 147, 150 have been fully considered and are persuasive. The rejection of claims 135, 136, 138, 139, 144, 147, 150 has been withdrawn because Bachiller et al. do not teach that foreign DNA has integrated into the genome of the sperm cell.

Applicant's arguments regarding 35 U.S.C §102(a), anticipated by Kim et al., 1997, see page 9 of Applicant's Response, August 30, 2004, with respect to claims 135, 136, 138, 139, 144, 145, 147, 150, 151, 152 have been fully considered and are persuasive. The rejection of claims 135, 136, 138, 139, 144, 145, 147, 150, 151, 152 has been withdrawn because Kim et al. teach in their *in vitro* studies that "liposome/DNA complexes can be bound into spermatozoa efficiently, but cannot be incorporated into their chromosome DNA (Kim et al., page 519, col. 1, lines 4-7)".

Applicant's arguments regarding 35 U.S.C §102(e), anticipated by Brinster, Patent No. 5,858,354, patented January 12, 1999, see page 10-11 of Applicant's Response, August 30, 2004, with respect to claims 135-145, 147-155 have been fully considered and are persuasive. The rejection of claims 135-145, 147-155 has been withdrawn because Brinster does not teach integration of a viral vector in the sperm genome.

Maintained Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 135, 137, 138, 140-143, 145-159 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Brinster and Zimmermann (1994, PNAS, USA, 91: 11298-11302, filed in First Office Action) in view of Vogel and Sarver (1995, Clinical Microbiology Reviews, 8:406-410), for reasons of record stated in the First Office Action, filed October 6, 2003.

The instantly claimed invention is to an *in vitro* method of introducing a transgene comprised of a nucleic acid sequence encoding a protein of interest operatively linked to a promoter, into a male germ cell, wherein the transgene is integrated into the genome of said germ cell.

Response to Arguments

Applicant's arguments filed August 30, 2004 have been fully considered but they are not persuasive.

The Examiner has pointed to Brinster and Zimmermann in the First Office Action for teaching that it was known in the art that embryonic stem (ES) cells could be genetically modified and that Brinster and Zimmermann suggest that spermatogonia, like ES cells, could be cultured and manipulated like ES cells,

and could then be used in a manner similar to ES cells for creating mice with germ line modifications. Applicants disagree with this assertion, as they believe that spermatogonia are distinct and have different properties. Because spermatogonia have biological differences from ES cells, the Applicants do not believe that there is any reason that spermatogonia could be transfected merely because ES cells have (Applicant's Response, page 11-12). The Examiner does not find the argument convincing because the Applicants manipulate spermatogonial tissue in the same way as Brinster and Zimmerman and add the method of transgenesis as proposed by Brinster and Zimmerman on page 11301, 2nd col., last parag.). At the time of filing, methods of introducing foreign DNA were well known in the art. These methods include lipofection and electroporation. Also at the time of filing, it was also well known that foreign DNA could be integrated into a host cell's genome via homologous and non-homologous recombination (e.g. see Cappechi, 1989, Trends in Genetics, 5: 70-76). For these reasons, there would have been a reasonable expectation of success that foreign DNA would have integrated into spermatogonia cells. While the Applicants assert that spermatogonia are different from ES cells, they provide no biological evidence as to what the difference is between the two cell types that spermatogonia would not integrate foreign DNA, while ES cells would. Further, while the Applicants cite Kim et al. and Bachiller et al. for teaching methods wherein transgenesis do not occur, Kim et al. and Bachiller et al. teach the method using non-viral DNA, which integrates less often in the genome than does viral DNA.

With regards to the embodiment of using viral DNA or virally derived DNA, an artisan at the time of filing would have been motivated to use viral DNA, as the art teaches that "unlike the previously cited studies of DNA plasmid-mediated delivery, in which the delivered genes remain unintegrated, gene transferred via retroviral vectors are inserted into the host chromosome, thereby ensuring the perpetuity of the genetic information in the target cells (Vogel and Sarver, 1995, Clinical Microbiology Reviews, 8: 406-410)."

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the method taught by Brinster and Zimmermann, for introducing transfected donor spermatogonia into recipient mouse and use such mouse for producing a transgenic mouse. An artisan of ordinary skill would have been motivated to use a viral vector, such as a retroviral vector, as a vehicle to introduce a transgene of interest, as Vogel and Sarver teach that retroviral vectors integrate into the host cell's genome.

There would have been a reasonable expectation of success given the teachings and results of Brinster and Zimmermann that describes the method of isolating spermatogonia, transfecting them with an exogenous transgene, and transplanting the transfected spermatogonia into a recipient mouse. There is nothing in the record and the applicants have not provided any evidence that an artisan would not have had success in providing a transgenic mouse following the methods taught by Brinster and Zimmerman.

Thus, the claimed invention as written was clearly *prima facie* obvious.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 160 is rejected under 35 U.S.C. 103(a) as being unpatentable over Brinster and Zimmermann (1994, PNAS, USA, 91: 11298-11302, filed in First Office Action) in view of Vogel and Sarver (1995, Clinical Microbiology Reviews, 8:406-410), as applied to claims 135, 137, 138, 140-143, 145-159, as described above, and in further view of Wivel and Walters (1993, Science, 262: 533-538).

Claim 160 depends on claim 135. The teachings of Brinster in view of Vogel as they apply to claim 135 are set forth in detain in the previous Office Action and discussed above.

While Brinster and Zimmermann, teach introduction of transfected donor spermatogonia into recipient mouse and use such mouse for producing a transgenic mouse and Vogel and Sarver teach that retroviral vectors integrate into the host cell's genome, neither teach the introduction of a polynucleotide encoding a gene product which is able to correct a gene disorder.

Wivel and Walters teach that there are some genetic diseases which are candidates for genetic intervention which involves the correction or prevention of genetic deficiencies. Wivel and Walters teach that monogenic deficiency diseases would be candidates for prevention by germ-line gene modification.

These include Lesch-Nyhan syndrome, Tay-Sachs disease, and metachomatic leukodystrophy (Wivel and Walters, page 535, 2nd col., 2nd parag.). Wivel and Walters teach that the genes of these diseases have been cloned and their mutations have been characterized. Wivel and Walters teach that somatic cell gene therapy, if applicable, would almost certainly require surgical intervention, and it would be difficult to postulate postpartum treatment of newborns affected with these disorders (Wivel and Walters, page 535, 2nd col. 2nd parag.). Wivel and Walters teach that Lesch-Nyhan disease results from a deficiency in hypoxantine-guanosine phosphoribosylase transerase (HPRT) gene (Wivel and Walters, page 535, 2nd col., 3rd parag.), that Tay-Sachs disease results from a mutation in *HEXA*, (Wivel and Walters, page 535, 2nd col., 4th parag.), and that metachromatic leukodystrophy is caused by the deficiency of arylsulfatase A (Wivel and Walters, page 535, 3rd col., 2nd parag.).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the method taught by Brinster and Zimmermann, for introducing transfected donor spermatogonia into recipient mouse and use such mouse for producing a transgenic mouse. An artisan of ordinary skill would have been motivated to use a viral vector, such as a retroviral vector, as a vehicle to introduce a transgene of interest, as Vogel and Sarver teach that retroviral vectors integrate into the host cell's genome. An artisan of ordinary skill in the art would also have been motivated to introduce a gene that would correct a monogenic deficiency disease such as Lesch-Nyhan syndrome, Tay-Sachs disease, or metachromatic leukodystrophy, as Wivel and

Walters point out that the genes have been cloned and the mutations have been characterized.

There would have been a reasonable expectation of success given the teachings and results of Brinster and Zimmermann that describes the method of isolating spermatogonia, transfecting them with an exogenous transgene, and transplanting the transfected spermatogonia into a recipient mouse. There is nothing in the record and the applicants have not provided any evidence that an artisan would not have had success in providing a transgenic mouse following the methods taught by Brinster and Zimmerman.

Thus, the claimed invention as written was clearly *prima facie* obvious.

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be

calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful; the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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JH

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER